Journal of Surgical Oncology 1999;70:126–129

Unexplained Decrease in Measured Oxygen Saturation by Pulse Oximetry Following Injection of Lymphazurin 1% (Isosulfan Blue) During a Lymphatic Mapping Procedure

ROBERT L. COLEMAN, MD,[1]* CHARLES W. WHITTEN, MD,[2] JOHN O'BOYLE, MD,[1] AND BOBBIE SIDHU, CRNA[2]

[1]*Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, University of Texas, Southwestern Medical Center, Dallas, Texas*

[2]*Department of Anesthesiology, University of Texas, Southwestern Medical Center, Dallas, Texas*

A rare case of alteration in measured pulse oximetry during a lymphatic mapping procedure for cervical carcinoma is reported. Over a 5-min period following injection of perilesional Lymphazurin 1% dye (3 ml total), a profound pulse oximetry desaturation was observed. Concomitant arterial blood gas determinations confirmed patient's well-being. Interaction of this agent's absorptive spectroscopy and wavelengths used to measure oxygen saturation by commercial pulse oximetry devices is suspected.

J. Surg. Oncol. 1999;70:126–129.

KEY WORDS: absorptive spectroscopy; sentinel node; cervical cancer; hemoglobin species

INTRODUCTION

Clinical utility for lymphatic mapping among patients with malignancy is increasingly being defined. Surgeons caring for patients with carcinomas of the breast, head and neck, vulva, and melanoma are now utilizing the technology to provide additional clinical data and tailor planned surgical interventions [1–5]. This procedure is performed by injecting the blue dye, Lymphazurin 1% (isosulfan blue, Ben Venue Laboratories, Richmond, VA) subcutaneously at the edge of the primary tumor. It is believed that isosulfan blue is selectively picked up by the regional lymphatics because, in aqueous solution, approximately 50% is weakly bound to serum protein. Lymphatic vessels and nodes are distinguishable from surrounding tissue by the resultant bright blue color. Adjunctive lymphoscintigraphy using filtered technetium sulfur colloid is also being evaluated in many of these patients [1–3,5]. Further staging and clinical management is based on the preoperative and/or intraoperative assessment of the primary draining node or group of nodes, otherwise referred to as the ''sentinel'' nodes. Melanoma patients, for example, are undergoing this procedure to determine which cohort will require complete lymphadenectomy as a part of primary resection [3,5]. Breast cancer patients are undergoing lymphatic mapping procedures in an attempt to identify those who may be spared standard axillary lymphadenectomy if the sentinel node pathology is negative [1].

In addition, lymphatic mapping trials are in progress to ascertain if the primary lymphatic drainage tributaries are reflective of the final nodal status for individual cancers [4,6].

Part of the success of these efforts has stemmed from reliability of the visible dye entering primary draining lymphatics with little consequence to the patient. Overall complication rates from these procedures varies from 0% to 1.5% (package insert) and are predominantly related to allergic reactions to the dye. Fortunately, few cases of circulatory collapse as a result of systemic anaphylaxis

*Correspondence to: Robert L. Coleman, MD, University of Texas, Southwestern Medical Center, Dallas J7.124, 5323 Harry Hines Blvd., Dallas, TX 75235–9032. Fax No.: (214) 648-8404.
E-mail: rcole1@mednet.swmed.edu

Accepted 4 December 1998

have been reported [7]. An observation that has not been reported with isosulfan blue is the effect that circulating or systemic absorption of this dye has on intraoperative pulse oximetry monitoring. Alteration in peripheral pulse oximetry determination due to systemic absorption has been reported with other vital dyes, such as methylene blue. Scheller et al. [8] reported that peripheral pulse oximetry was falsely and transiently lowered among healthy volunteers injected intravenously with 5 ml of 1% methylene blue. This effect was not observed with two other dyes, indigo carmine 0.8% (5 ml) or indocyanine 0.25% (5 ml) [8]. The authors demonstrated that this effect was due to interfering absorptive spectroscopy from the blood at the precise wavelengths used for estimating hemoglobin saturation. We report a rare case where Lymphazurin 1% administration during a lymphatic mapping procedure resulted in an acute decrease in measured pulse oximetry saturation.

MATERIALS AND METHODS

A 44-year-old Hispanic female diagnosed with stage IB_1 cervical cancer was scheduled for an abdominal radical hysterectomy with pelvic and paraortic lymphadenectomy as primary treatment. Her past medical history was significant only for hypertension, which was well-controlled with verapamil. She reported no allergies to medication or foods. She had no history of intrinsic atopy. Preoperative physical examination was remarkable only for a 3.5 × 3.5 cm exophytic cervical carcinoma, predominantly replacing the cervical portio. No uterosacral, vaginal, or parametrial disease was evident and preoperative computed tomography revealed no suspicious lymphadenopathy. She agreed to participate in a clinical trial of intraoperative lymphatic mapping of patients with cervical cancer undergoing lymphadenectomy. This trial is approved by the Institutional Review Board and conducted in accordance with the Helsinki Declaration of 1975, as revised in 1983.

RESULTS

Preoperative vital signs were as follows: blood pressure 138/92; pulse, 81; respiratory rate, 12; temperature, 36.2°C; preinduction O_2 saturation (SpO_2) on room air, 98% (pulse oximeter: Oxypleth®, Novametrixs Medical Systems, Wallingford, CT). The patient arrived in the operating room and received 30 ml of bicitra and 10 mg of metoclopropramide IV, followed by midazolam 2 mg i.v., during placement of monitors. Anesthetic induction consisted of 250-mcg fentanyl, 350-mg sodium thiopental, and 100 mg of succinylcholine. Maintenance anesthesia consisted of isoflurane in a 60/40 mixture of nitrous oxide/oxygen with supplemental doses of fentanyl to maintain hemodynamic stability. Rocuronium was utilized for muscle relaxation. Approximately 65 min after anesthetic induction and approximately 25 min after the onset of the surgical procedure, the patient's uterine cervix was injected with 1.5 ml of Lymphazurin 1% (isosulfan blue) at the lateral periphery through a 22-gauge spinal needle (total injection volume was 3 ml). Vital signs were stable and an SpO_2 was 98% at an FiO_2 of 0.4. This procedure was performed with the patient in a low lithotomy position, and after celiotomy and preliminary retroperitoneal dissection was initiated.

According to our protocol, the pararectal and paravesical spaces were developed but division of the round ligament or any parametrial tissue was withheld until sentinel node identification was made. On the patient's left fornix, perforation of the needle into the lateral cul-de-sac was observed with deposition of approximately 1.5 ml of isosulfan blue dye into the left parametrial tissue and cul-de-sac peritoneum. This fluid was suctioned immediately on recognition. Sentinel node identification on this left side was hindered by the extensive staining of the tissue. On the right side, a primary sentinel node was identified at the level of the bifurcation of the common iliac artery. Histologically, this node was negative for metastatic disease, as were all of her final lymphatic specimens. Five minutes after injection, the patient had a gradual decrease in her SpO_2 to 89%–90%, and her face, the only skin readily visible, became blue-green in color. At this point, the patient was hyperventilated with 100% oxygen without significant improvement in her SpO_2. She was noted to have equal and bilateral breath sounds, and there was no other readily identifiable cause for this dramatic decrease in her SpO_2.

During this episode, the patient was noted to have no changes in her electrocardiogram, and her vital signs were otherwise stable. The working diagnosis was a methemoglobinemia-type response to the dye. An arterial blood gas obtained concomitantly with the desaturation on 40% O_2 returned a pH of 7.51, a PCO_2 of 29, a PO_2 of 84 with a bicarbonate of 23.5 and an O_2 saturation of 97.6%. Over the next 5 min her SpO_2 slowly returned to 99% on this FiO_2. Repeat arterial blood gas demonstrated concomitant findings with the measured pulse saturation. Given these reassuring findings and a reflective blood gas, we proceeded with an otherwise uneventful radical hysterectomy and pelvic and paraortic lymphadenectomy.

DISCUSSION

Lymphazurin 1% (isosulfan blue) is an injectable blue dye with a molecular weight of 563.13 da. Evidence suggests that approximately 50% of isosulfan blue, in aqueous solution, is weakly bound to serum proteins, which imparts its characteristic lymphatic tropism. It is the dye most commonly used to identify lymphatic vessels as a means of performing lymphatic mapping. It has also been used to identify lymphatics for catheterization in patients undergoing lymphangiography. Fortunately, its side effect profile is modest and generally limited to

hypersensitivity reactions. We report a case in whom the systemic absorption of the dye may have led to a false lowering of pulse oximetry, which we believe occurred as a result of interference with normal pulse oximetry recording.

Pulse oximetry is a noninvasive modality providing continuous estimations of peripheral tissue oxygen saturation and is a ubiquitous component of modern operative anesthesiology. It functions via determination of the concentrations of oxyhemoglobin and reduced hemoglobin species by measuring the absorbance of light at two wavelengths, 660 and 940 nm, respectively. The concentration of one hemoglobin species can be determined from each light wavelength whose absorption is measured. A laboratory co-oximeter, which uses four or more wavelengths, can measure the concentrations of reduced hemoglobin (Hb), oxyhemoglobin (O_2Hb), methemoglobin (MetHb), and carboxyhemoglobin (COHb) by using the sample light absorbance data and comparing this data against known absorbance spectra of the various hemoglobin species [9]. If all four hemoglobins are present in a significant concentrations, then an oximeter must utilize at least four wavelengths to determine the concentration of any of the four species. The pulse oximeter is a two-wavelength oximeter that functions in vivo. It eliminates the effects of the solid tissues positioned between the light source and detector by determining the fluctuating or ''AC'' component of the absorbent signal. At each of its two wavelengths, the pulse oximeter divides the AC signal by the corresponding DC component to obtain a pulse-added absorbance. It then calculates the ratio of the two pulse-added absorbances, and this ratio is related to SaO_2 by a built-in calibration algorithm based on volunteer data [9]. The resulting pulse oximeter saturation is referred to as the SpO_2. Two animal studies have characterized pulse oximeter behavior during dyshemoglobinemias. In one of these, dogs were exposed to carbon monoxide over a 3- to 4-hr interval [10]. At a carboxyhemoglobin level of 70%, the SpO_2 values were roughly 90% while the actual SaO_2 was 30%. The pulse oximeter in this situation is unable to determine the contribution of carboxyhemoglobin saturation to total saturation and, therefore, grossly overestimates oxyhemoglobin saturation. In a similar experiment, dogs breathing 100% O_2 and exposed to increasing concentrations of methemoglobin consistently demonstrated overestimated SpO_2 that was proportional to concentration of methemoglobin up to 35%. At this level, SpO_2 values did not fall below 85% with increasing methemoglobin unless inspired FiO_2 levels were reduced [11]. If abnormal hemoglobin species can affect the accuracy of pulse oximetry through this mechanism, it is probable that intravenous dyes injected during surgery could also influence pulse oximetry. A recent study by Scheller et al. [8] confirms this speculation. These authors demonstrated that injection with 5 ml of intravenous methylene blue can cause large, rapid decreases in SpO_2 without decreases in the actual SaO_2. In this study, the falsely lowered SpO_2 values were attributed to absorbance interference at the 660-nm site where oxyhemoglobin is measured. This is the peak absorbance site for methylene blue as well. In effect, measurement of oxyhemoglobin is reduced due to competition at this wavelength and, thus, total calculated saturation (SpO_2) is reduced. The observed phenomenon was transient and related to the site of measurement (proximal vs. distal extremity). This study demonstrated, in addition, that indocyanine green could also cause false decreases in SpO_2, albeit to a much lesser degree. Other dyes studied, fluorescein and indigo carmine, appeared to have little effect.

By way of comparison, isosulfan blue has an absorbance peak of 646 nm. It could be hypothesized that a ''methylene blue-type'' of interaction between the pulse oximetry and the transient systemic absorption of isosulfan blue occurred in this patient. Confirmatory and reassuring oxygen saturation obtained by arterial blood sampling during the acute fall in SpO_2 suggests that the reading was inaccurate. Although this dye has a predilection for lymphatic channels once injected, it is likely that this patient sustained a significant vascular absorption from spill onto the peritoneal surface and in the highly vascular parametrium. Her transient blue-green skin hue and acute desaturation raised several working differential diagnoses, including pneumothorax, pulmonary embolus, and malposition of the endotracheal tube, all of which were systematically ruled out. We would suggest that this effect be considered in patients suffering acute desaturation while undergoing lymphatic mapping but that measures of more profound consequence continue to be addressed first. As was observed in this case and in the series by Scheller et al. [8], the phenomena is transient (3–5 min). Primary excretion of isosulfan blue is biliary (90%) and thus patients with hepatobiliary impairment may have sustained effects. The maximal suggested administration is 3.0 ml (30-mg isosulfan blue).

We believe the observed effect is uncommon, since acute, systemic levels of isosulfan blue does not readily occur in routine lymphatic mapping procedures. However, if the tumor is highly vascular or located within highly vascular surrounding tissues, the possibility of significant vascular uptake is increased. As the clinical utility of lymphatic mapping continues to be explored, it is likely that these effects will be increasingly observed. Anesthesiologists and surgeons need to be aware of the potential effects these dyes can have on saturation monitoring so that the most appropriate measures can be taken in the operating room or surgery suite when a similar situation arises.

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